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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/376,911	08/18/1999	FRANCIS MICHON	3842-4043US1	7105

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EXAMINER
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ART UNIT	PAPER NUMBER
1645	17

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/376,911	Michon et al.
Examiner	**Art Unit**
S. Devi, Ph.D.	1645

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jun 17, 2002*.

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-63* is/are pending in the application.

4a) Of the above, claim(s) *6, 7, 29-37, and 41-58* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-5, 8-28, 38-40, and 59-63* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *14.*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

RESPONSE TO APPLICANTS' AMENDMENT

Applicants' Amendments

1) Acknowledgment is made of Applicants' amendment, corrected amendment and supplemental amendments filed 04/23/02 (paper no. 12) and 06/17/02 (paper no. 15 and 16) in response to the non-final rejection mailed 01/28/02 (paper no. 11).

Status of Claims

2) Claims 1-5, 8-22, 24-26 and 37-40 have been amended via the amendment filed 04/23/02.

Claims 1-5, 8-22, 24-26 and 37-40 have been amended via the corrected amendment filed 06/17/02.

Claims 1, 4, 15, 16 and 39 have been amended via the supplemental amendment filed 06/17/02.

New claims 59-63 have been added via the supplemental amendment filed 06/17/02.

Claims 1-63 are pending.

Claims 1-5, 8-28, 37-40 and 59-63 encompassing group B streptococcus type III polysaccharide conjugate, are under examination.

Information Disclosure Statement

3) Acknowledgment is made of Applicants' information disclosure statements filed 06/17/02 (paper no. 14). The information referred to therein has been considered and a signed copy is attached to this Office Action (paper no. 17).

Prior Citation of Title 35 Sections

4) The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

Prior Citation of References

5) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

Objection(s) Withdrawn

6) The objection to the specification made in paragraph 7(b) of the Office Action mailed

01/28/02 (paper no. 11) is withdrawn in light of Applicants' amendments to the specification.

7) The objection to the specification made in paragraph 7(d) of the Office Action mailed 01/28/02 (paper no. 11) is withdrawn in light of Applicants' amendments to the specification.

8) The objection to claims 37 and 38 made in paragraph 23(a) of the Office Action mailed 01/28/02 (paper no. 11) is withdrawn in light of Applicants' amendment to the base claim.

9) The objection to claims 5 and 8 made in paragraph 23(b) of the Office Action mailed 01/28/02 (paper no. 11) is withdrawn in light of Applicants' amendment to the claims.

10) The objection to claim 15 made in paragraph 23(c) of the Office Action mailed 01/28/02 (paper no. 11) is withdrawn in light of Applicants' amendment to the claim.

11) The objection to claim 26 made in paragraph 23(d) of the Office Action mailed 01/28/02 (paper no. 11) is withdrawn in light of Applicants' amendment to the claim.

12) The objection to claims 22 and 26 made in paragraph 23(e) of the Office Action mailed 01/28/02 (paper no. 11) is withdrawn in light of Applicants' amendment to the claims.

13) The objection to claim 5 made in paragraph 23(f) of the Office Action mailed 01/28/02 (paper no. 11) is withdrawn.

14) The objection to claim 15 made in paragraph 23(g) of the Office Action mailed 01/28/02 (paper no. 11) is withdrawn in light of Applicants' amendment to the claim.

Objection(s) Maintained

15) The objection to the specification made in paragraph 7(a) of the Office Action mailed 01/28/02 (paper no. 11) is maintained for reasons set forth therein. Applicants have not submitted a clean and a marked-up version of the first paragraph of the specification to replace the current first paragraph of the specification with.

16) The objection to the specification made in paragraph 7(c) of the Office Action mailed 01/28/02 (paper no. 11) is maintained for reasons set forth therein and herebelow. The recitation in claim 16: "N-propionated polysaccharide" or "N-propionated oligosaccharide" does not have antecedence in the specification.

Applicants point to page 8, lines 25-29 under section 2. N-Acryloylation of the Polysaccharide as providing support for "the process of making N-propionated saccharides".

However, this part of the specification does not provide descriptive support for the phrase: "the process of making N-propionated saccharides". Applicants further assert that "N-acrylolylated polysaccharide (oligosaccharide) is equivalently described within the art as an N-propionated polysaccharide (oligosaccharide)". However, no art or an authoritative textbook reference is submitted that equates "N-acryloylation" to "N-propionation".

Rejection(s) Withdrawn

17) The rejection of claims 25 and 40 made in paragraph 9 of the Office Action mailed 01/28/02 (paper no. 11) under 35 U.S.C § 112, first paragraph, as being non-enabled with regard to the scope, is withdrawn.

18) The rejection of claims 1 and 16 made in paragraph 11(a) of the Office Action mailed 01/28/02 (paper no. 11) under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn.

19) The rejection of claims 2-5, 8 and 11-13 made in paragraph 11(b) of the Office Action mailed 01/28/02 (paper no. 11) under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendments to the claims.

20) The rejection of claims 38-40 made in paragraph 11(c) of the Office Action mailed 01/28/02 (paper no. 11) under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendments to the claims.

21) The rejection of claim 20 made in paragraph 11(e) of the Office Action mailed 01/28/02 (paper no. 11) under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.

22) The rejection of claim 24 made in paragraph 11(f) of the Office Action mailed 01/28/02 (paper no. 11) under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.

23) The rejection of claims 25 and 40 made in paragraph 11(g) of the Office Action mailed 01/28/02 (paper no. 11) under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claims.

24) The rejection of claims 5 and 15 made in paragraph 11(h) of the Office Action mailed

01/28/02 (paper no. 11) under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to claim 5.

25) The rejection of claims 9, 10, 14 and 18-28 made in paragraph 11(i) of the Office Action mailed 01/28/02 (paper no. 11) under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the base claim(s).

26) The rejection of claims 1-4, 8, 11-14, 22 and 26-28 made in paragraph 13 of the Office Action mailed 01/28/02 (paper no. 11) under 35 U.S.C. § 102(b) as being anticipated by Roy *et al.* (*J. Chem. Soc. Chem. Commun.* 264-265, 1993) (Roy *et al.*, 1993), is withdrawn in light of Applicants' amendments to the claims and/or the base claim(s).

27) The rejection of claims 1-3, 14 and 22 made in paragraph 14 of the Office Action mailed 01/28/02 (paper no. 11) under 35 U.S.C. § 102(b) as being anticipated by Roy *et al.* (*J. Chem. Soc. Chem. Commun.* 536-538, 1991) (Roy *et al.*, 1991), is withdrawn in light of Applicants' amendments to the claims and/or the base claim(s).

28) The rejection of claims 1-4, 8, 11-14, 16, 17 and 19-22 made in paragraph 15 of the Office Action mailed 01/28/02 (paper no. 11) under 35 U.S.C. § 102(b) as being anticipated by Pon RA (*The Study of Polysialic acid Conjugates*. Master's Thesis, University of Ottawa, pp. 1-251, UMI Dissertation Services, 1992), is withdrawn in light of Applicants' amendments to the claims and/or the base claims.

29) The rejection of claims 1-3, 8, 11-14 and 22 made in paragraph 16 of the Office Action mailed 01/28/02 (paper no. 11) under 35 U.S.C. § 102(b) as being anticipated by Roy *et al.* (*J. Chem. Soc. Chem. Commun.* 1709-1711, 1990) (Roy *et al.*, 1990), is withdrawn in light of Applicants' amendments to the claims and/or the base claims.

30) The rejection of claims 1-3, 8, 11-14 and 22 made in paragraph 17 of the Office Action mailed 01/28/02 (paper no. 11) under 35 U.S.C. § 102(b) as being anticipated by Romanowska *et al.* (*Methods in Enzymol.* 242: 90-101, 1994 - Applicants' IDS), is withdrawn in light of Applicants' amendments to the claims and/or the base claims.

31) The rejection of claims 1-4, 11-14 and 22 made in paragraph 18 of the Office Action mailed 01/28/02 (paper no. 11) under 35 U.S.C. § 102(b) as being anticipated by Auzanneau *et*

al. (*Bioorg. Medicinal Chem.* 4: 2003-2010, 1996), is withdrawn in light of Applicants' amendments to the claims and/or the base claim(s).

32) The rejection of claims 1-3, 8 and 11-14 made in paragraph 19 of the Office Action mailed 01/28/02 (paper no. 11) under 35 U.S.C. § 102(b) as being anticipated by Roy *et al.* (*Bioorg. Medicinal Chem. Lett.* 2: 911-914, 1992) (Roy *et al.*, 1992), is withdrawn in light of Applicants' amendments to the claims and/or the base claim(s).

Rejection(s) Maintained

33) The rejection of claims 18 and 20 made in paragraph 8 of the Office Action mailed 01/28/02 (paper no. 11) under 35 U.S.C § 112, first paragraph, as being non-enabled with regard to the scope, is maintained for reasons set forth therein and herebelow.

Applicants contend that the instant specification at page 10 provides descriptive support for a method of conjugation being conducted at a neutral pH of about 7.0. Applicants allege that the Office does not mention anything about conjugation of cysteine-rich protein to polysaccharides. Applicants allege that the enablement rejection is improper, because the Office has not provided a basis for which to reject the truth or accurarcy of the specification's guidance for the conjugation of cysteine-rich proteins at neutral pH. Applicants point to MPEP § 2164.04 and state that it is incumbent upon the Office to explain why it doubts the truth or accuracy of any statement in a 'supporting disclosure' and to 'back up' assertions of its own with evidence and reasoning which is inconsistent with the contested statement. Applicants acknowledge Ramanowska's teaching that only very slow coupling in takes place in phosphate buffers, but submit that there was coupling nevertheless.

Applicants' arguments have been carefully considered, but are non-persuasive. Contrary to Applicants' assertion, the Office provided sufficient evidence, reasoning and multiple 'supporting disclosures' to 'back up' the Office's position that the descriptive support in the specification is not commensurate in scope with the evidentiary support. The following prior art references were provided by the Office to show that the full scope of the claimed invention is not enabled: Romanowska *et al.* (*Methods in Enzymol.* 242: 90-101, 1994); Roy *et al.* (*J. Chem. Soc., Chem. Commun.* 1709-1711, 1990); Roy *et al.* (*J. Chem. Soc., Chem. Commun.* 536-538,

1991); and Pon (*The Study of Polysialic acid Conjugates*. Master's Thesis, University of Ottawa, pp. 1-251, UMI Dissertation Services, 1992). The detailed reasoning provided by the Office is reproduced herebelow:

> The art indicates that conjugation by Michael addition is carried out in the alkaline range, i.e., above 9.0 in an appropriate buffer, such as, borate or carbonate buffer. For instance, Romanowska *et al.* (*Methods in Enzymol.* 242: 90-101, 1994 - Applicants' IDS) used a pH of 8.5, 9.5 and 10.5 for this type of conjugation (see page 94) and found a pH of 10.0 or 10.5 to be optimal for coupling, which pH prevented protein degradation (see page 101). Roy *et al.* (*J. Chem. Soc., Chem. Commun.* 1709-1711, 1990) teach that N-acryloylated oligosaccharide can be covalently conjugated to a protein by Michael reaction at a pH greater than 8.0 to 8.5 and at 10.5 (see page 1710). Roy *et al.* (*J. Chem. Soc., Chem. Commun.* 536-538, 1991) teach that even at a pH of 8.0 or 9.0 in phosphate buffer, the Michael reaction did not furnish appreciable conjugation; the reaction however proceeded smoothly at these two pH in carbonate buffer. Roy *et al.* (*J. Chem. Soc., Chem. Commun.* 536-538, 1991) also teach that a very small amount of carbohydrate was conjugated in borate buffer at pH 8.0 (see paragraph bridging pages 537 and 538). Pon (*The Study of Polysialic acid Conjugates*. Master's Thesis, University of Ottawa, pp. 1-251, UMI Dissertation Services, 1992) teaches that phosphate buffers at various pH values did not prove satisfactory during the conjugation process (see page 147, lines 2-4).
>
> Undue experimentation would have been required to practice the invention as claimed due to the lack of guidance/evidence, lack of working examples, the uncertainty with regard to conjugation by Michael addition taking place at a non-alkaline pH of 7.0 and in a phosphate buffer medium and the quantity of experimentation necessary.

It is noted that Applicants have **not** addressed the Office's reasoning as supported by the prior art disclosures of Roy *et al.* (*J. Chem. Soc., Chem. Commun.* 1709-1711, 1990); Roy *et al.* (*J. Chem. Soc., Chem. Commun.* 536-538, 1991) and Pon (*The Study of Polysialic acid Conjugates*. Master's Thesis, University of Ottawa, pp. 1-251, UMI Dissertation Services, 1992). Claims 18 and 20, depend from claim 16. Claim 16, as amended currently, encompasses a conjugate which is required to elicit "protective antibodies". A conjugate as claimed in claims 18 and 20 wherein the coupling is conducted at a pH of about 7.0 and in phosphate buffer, which conjugate elicits "protective antibodies" is clearly not enabled. In order for a conjugate to be protective, the process of conjugation or coupling has to take place effectively under conditions that are accepted in the art to be satisfactory, or under conditions that are shown within the instant specification to be satisfactory such that the protective epitopes of the polysaccharide, oligosaccharide and/or the protein are retained. As explained in paragraph 8 of the Office Action mailed 01/28/02 (paper no. 11) and above, several published prior art references demonstrated that N-acryloylated oligosaccharide can be covalently conjugated to a protein by Michael reaction at a pH **greater** than 8.0 to 8.5 and at 10.5, and that even at a pH of 8.0, the Michael reaction did **not** furnish

appreciable conjugation. Roy *et al.* (*J. Chem. Soc., Chem. Commun.* 536-538, 1991) expressly taught that a very small amount of carbohydrate was conjugated at pH 8.0. Pon (*The Study of Polysialic acid Conjugates*. Master's Thesis, University of Ottawa, pp. 1-251, UMI Dissertation Services, 1992) expressly taught that phosphate buffers at various pH values did not prove satisfactory during the conjugation process. *Arguendo*, even if one assumed that the Michael reaction does take place to some extent at pH 7.0, it is unlikely that the resultant poorly conjugated polysaccharide or oligosaccharide would elicit 'protective antibodies'. The instant specification does not demonstrate that the claimed conjugate synthesized at a coupling pH of about 7.0 would maintain the needed conformation or retain the necessary epitopes that elicit a 'protective antibodies'. Absent such an evidence, the rejection stands.

34) The rejection of claims 37-40 made in paragraph 10 of the Office Action mailed 01/28/02 (paper no. 11) under 35 U.S.C § 112, first paragraph, as being non-enabled with regard to the scope, is maintained for reasons set forth therein and herebelow.

Applicants state that they have amended claim 37 such that claims 37-40 now pertain to conjugate vaccines comprising N-acryloylated polysaccharides or oligosaccharides that provide protective immunity against at least one member of the genus of the organism from which the polysaccharide or oligosaccharide component of the polysaccharide- or oligosaccharide-protein conjugate was obtained.

Applicants' argument has been considered, but is not persuasive. As amended, the conjugate recited in the claims is now required provide 'protective immunity against at least one member of a genus of an organism from which the polysaccharide or oligosaccharide component of the polysaccharide-protein conjugate or oligosaccharide-protein conjugate was obtained'. The recitation "organism" encompasses a fungus, a parasite, a bacterium, a yeast, a virus, a pathogen, a non-pathogen etc., The recitation "at least one member of a genus of an organism" encompasses a myriad of homologous and heterologous members of a bacterial, fungal or parasitic genus, both pathogenic and normal commensal. The term 'at least' is equivalent to any number that exceeds one. For instance, the genus '*Streptococcus*' encompasses several members such as, *Streptococcus pyogenes*, *Streptococcus pneumoniae*, *Streptococcus faecalis*, *Streptococcus viridans*, Group B *Streptococcus* (GBS), Group A *Streptococcus*, type III GBS,

type II GBS, type V GBS etc. However, a type III GBS capsular polysaccharide-protein conjugate, or an *E. coli* O111 liopolysaccharide-protein conjugate according to the invention for example, would not and cannot be expected to provide protective immunity against any number of members of the genus *Sreptococcus* or *E. coli* other than type III GBS or *E. coli* O111 because of the immunological or biological specificity of the polysccharide or lipopolysaccharide used in the conjugate. Absent a showing otherwise, the rejection stands.

35) The rejection of claims 3-5 made in paragraph 11(d) of the Office Action mailed 01/28/02 (paper no. 11) under 35 U.S.C. § 112, second paragraph, as being indefinite, is maintained for reasons set forth therein.

36) The rejection of claims 1 and 8-10 made in paragraph 21 of the Office Action mailed 01/28/02 (paper no. 11) under 35 U.S.C § 103(a) as being unpatentable over Pon RA (*The Study of Polysialic acid Conjugates*. Master's Thesis, University of Ottawa, pp. 1-251, UMI Dissertation Services, 1992) in view of Blake *et al.* (US 5,439,808), is maintained for reasons set forth therein and herebelow.

37) The rejection of claims 1, 16 and 22-24 made in paragraph 22 of the Office Action mailed 01/28/02 (paper no. 11) under 35 U.S.C § 103(a) as being unpatentable over Pon RA (*The Study of Polysialic acid Conjugates*. Master's Thesis, University of Ottawa, pp. 1-251, UMI Dissertation Services, 1992) and Blake *et al.* (US 5,439,808), is maintained for reasons set forth therein and herebelow.

Applicants contend that Pon does not provide any evidence that a 15% N-acryloylated colominic acid-comprising conjugate, let alone any 'protein glycoconjugate' produced by Michael-type additions, can elicit a 'productive' response. Applicants assert that Pon's conjugates do not possess the same structural characteristics as the claimed conjugates, i.e., where "the protein component of the conjugates are coupled to either bacterial proteins or synthetic proteins containing lysine or cysteine residues". Applicants acknowledge that Pon's first conjugate consists of 15% N-acryloylated colominic acid conjugated to BSA or to IgG (see second full paragraph on page 8 of Applicants' amendment filed 06/17/02). Applicants contend that Pon's first model conjugate comprises porcine or bovine protein components, but not bacterial or synthetic protein components. Applicants acknowledge that the other three types of

conjugates contain N-acryloylated derivatives conjugated to BSA or TT in 'essentially the same manner', yet contend that Figure 4.9 shows that these derivatives are not de-N-acetylated and re-N-acryloylated at de-N-acetylated termini. Applicants further make the following statement (see last full paragraph on page 9 of Applicants' amendment filed 06/17/02):

> In contrast, claim 1 of the instant application recites "**at least 50%** of the N-propionated saccharides are de-N-acetylated", and claim 16 recites "wherein the polysaccharide or oligosaccharide is **at least 50%** de-N-acetylated". [Emphasis added].

Applicants' arguments have been carefully considered, but are non-persuasive. Base claims 1 and 16, and dependent claims 22-24 do not exclude a conjugate that consists of "15% N-acryloylated" polysaccharide or oligosaccharide conjugated to a bacterial or synthetic protein containing lysine or cysteine residues. Applicants' reference to "the protein component" of their conjugates being "coupled to either bacterial proteins or synthetic proteins containing lysine or cysteine residues" is not understood, since instant claims are directed to a polysaccharide-protein or oligosaccharide-protein conjugate, as opposed to a protein-protein conjugate. Applicants' discussion of a 'productive response' is not understood. It is also not understood which Figure 4.9 of Pon Applicants are referring to. As Applicants acknowledge, one of Pon's conjugates does consist of 15% N-acryloylated colominic acid conjugated to BSA or to IgG. It was well within the realm of routine experimentation to increase the percent N-acryloylation of colominic acid to the desired degree. Replacement of a non-bacterial protein carrier, advantageously, with a bacterial protein carrier in Pon's conjugate was also a matter of routine experimentation. Pon does not teach that a conjugate consisting of 15% N-acryloylated polysaccharide or oligosaccharide induces non-protective antibodies. It is noted that Pon's N-acryloylated colominic acid did show strong precipitation with H.46 (see Table 5-3; and page 205), an antibody that has been shown in the art to confer passive protection againt *E. coli* K1 infection (see section 'Relevant Prior Art' below). This is evidence that the N-acryloylated colominic acid in Pon's conjugate maintains its protective epitope and is capable of reacting with the protective H46 antibody. Contrary to Applicants' assertion, neither claim 1 nor claim 16, as amended, includes the recitation "at least 50%" to indicate the degree de-N-acetylation and N-acryloylation or N-propionation. As set forth in paragraphs 21 and 22 of the Office Action mailed 01/28/02, Blake *et al.* taught the routine use of recombinant bacterial proteins in the production of

polysaccharide-protein conjugates. It is noted that Applicants do not deny that Blake *et al.* taught the routine use of recombinant bacterial proteins in the production of polysaccharide-protein conjugates. Pon's conjugate as modified by Blake *et al.* meet the claim limitations and is viewed as the same as the claimed conjugate. Although the applied prior art does not expressly recite the ability of the conjugate to produce protective antibodies, Pon's conjugate as modified by Blake *et al.* is viewed as the same as the Applicants' conjugate. The Office's position that Pon's conjugate as modified by Blake *et al.* is the same as the Applicants' conjugate is based upon the fact that every structural characteristic overlapping in Applicants' disclosure and Pon's conjugate as modified by Blake *et al.* are the same. In spite of the fact that Pon *et al.* is silent about the protective ability of the conjugate, structurally there is sufficient overlap to reasonably conclude that the prior art conjugate is one and the same as the Applicants' conjugate. Since the prior art conjugate is structurally the same as the conjugate encompassed in instant claims, it is expected to have the same protective ability as that of the Applicants' conjugate. The rejection stands.

New Rejection(s)

Applicants are asked to note the following new rejection(s) made in this Office Action. The new rejection(s) is necessitated by Applicants' amendments to the claims and/or the base claim(s) and the submission of new claims.

Rejection(s) under 35 U.S.C. § 112, First Paragraph

38) Claims 1-5, 8-28, 37-40 and 59-63 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

Instant claims include the limitations: "N-propionated saccharide"; "N-propionated saccharide is de-N-acetylated and N-acryloylated at the de-N-acetylated terminus"; "directly coupled at a beta position of a propionate moiety". However, there appears to be no descriptive support in the instant specification for such limitations. Applicants point to page 7, section A of the specification and state that it provides support for the new limitation: "N-propionated saccharide". However, no such descriptive support can be found in this part of the specification for this broader limitation. The description in section A on page 7 of the specification is limited to

'polysaccharides' and 'oligosaccharides'. Applicants point to page 10, lines 6-14 of the specification and state that it provides support for the new limitation: "and wherein the N-propionated saccharide is de-N-acetylated and N-acryloylated at the de-N-acetylated terminus" in claim 1. However, the description at lines 6-14 on page 10 of the specification is not supportive of an N-propionated saccharide being de-N-acetylated and N-acryloylated at the de-N-acetylated terminus. The recitations "at a de-N-acetylated terminus" and "coupling at a beta-position of a propionate moeity" in claim 16 do not find descriptive support at lines 6-14 on page 10 and in Example 2. Therefore, the limitations identified above in the claims are considered to be new matter. *In re Rasmussen*, 650 F2d 1212 (CCPA, 1981). New matter includes not only the addition of wholly unsupported subject matter but also, adding specific percentages or compounds after a broader original disclosure, or even omission of a step from a method. See M.P.E.P 608.04 to 608.04(c).

Applicants are respectfully requested to remove the new matter from the claim(s), or point to the page and line number in the specification where support for such limitations can be found.

Rejection(s) under 35 U.S.C. § 112, Second Paragraph

39) Claims 1-5, 8-28, 37-40 and 59-63 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite, for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

(a) Claims 1 and 16 are vague and indefinite in the recitation "directly coupled to" and "directly coupling" respectively, because it is unclear what does this limitation encompass. The term is not defined in the specification. What does or what does not 'direct coupling' involve is not understood. It is not clear whether or not this limitation represents covalent coupling or non-covalent coupling.

(b) Claims 4, 15, 59, 61 and 63 lack antecedent basis for the recitation: "The conjugates according to claim 1" [Emphasis added]. Claims 4, 15, 59, 61 and 63 depend from claim 1 which is directed to "A conjugate", but not more than one conjugate.

(c) Claims 60 and 62 lack antecedent basis for the recitation: "The conjugates according to claim 16". Claims 60 and 62 depend from claim 16 which is directed to a "conjugate", but not more than one conjugate.

(c) Claim 4 is incorrect and/or redundant in the recitation "the the" saccharide (see line 1).

(d) Claims 59 and 61 lack antecedent basis for the recitation: "the saccharides are". Claims 59 and 61 depend from claim 1 which recites a "saccharide", but not saccharides.

(e) Claim 1, as amended, includes the new limitation: "the N-propionated saccharide directly coupled to the protein at the ... position of the propionate moiety elicits protective antibodies". It is unclear what are these antibodies protective against. In other words, the specificity of these antibodies is not understood. Are these protective antibodies saccharide-specific or protein-specific? Are these protective antibodies protective against an allergic condition, a malignant condition, an autoimmune condition, a virus, a fungus, or a bacterial pathogen? The limitations 'polysaccharide', 'oligosaccharide' and 'saccharide' broadly encompass a polysaccharide, oligosaccharide or saccharide of any source, including of plant, animal, nature and self origin. A self polysaccharide for example is unlikely to induce protective antibodies. If one used a plant polysaccharide in the claimed conjugate, it is not clear what would the resultant antibodies be protective against.

(f) Claim 16 includes the limitation: "conjugate that elicits protective antibodies". It is unclear what these antibodies are protective against. The specificity of these antibodies is not understood. Are these saccharide-specific antibodies or protein-specific antibodies? Are these antibodies protective against an allergic condition, a malignant condition, a virus, a fungus, or a bacterial pathogen? The limitations 'polysaccharide', 'oligosaccharide' or 'saccharide' broadly encompass a polysaccharide, oligosaccharide or saccharide of any source, including of plant, animal, nature and self origin. A self polysaccharide for example is unlikely to induce protective antibodies. If one used a plant polysaccharide in the claimed conjugate, it is not clear what would the resultant antibodies be protective against.

(g) Claim 16 is vague and indefinite in the recitation: "antibodies produced by a method comprising: A) ..... B).....C)", because it is unclear how "antibodies" can be produced by the method steps delineated in parts A), B) and C) of claim 16. It is suggested that Applicants replace the recitation "antibodies produced by" with --antibodies, wherein said conjugate is produced by--.

(h) Claims 2-5, 8-15, 17-28, 37-40 and 59-63, which depend directly or indirectly from claim 1 or claim 16, are also rejected under 35 U.S.C. § 112, second paragraph, as being indefinite, because of the vagueness or indefiniteness identified above in the base claim(s).

Rejection(s) under 35 U.S.C. § 103

40) Claims 1-4, 11-14, 16, 17, 19-22, 26-28, 37-39 and 59-63 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Pon RA (*The Study of Polysialic acid Conjugates*. Master's Thesis, University of Ottawa, pp. 1-251, UMI Dissertation Services, 1992) and Blake *et al.* (US 5,439,808).

See paragraphs 15, 21 and 22 of the Office Action mailed 01/28/02 (paper no. 11) and paragraph 37 above for a detailed teaching of Pon, and/or Pon as modified by Blake *et al.*

With regard to the variable percentages of N-acryloylation or de-N-acetylation of the polysaccharide or oligosaccharide, the optimization of degree of N-acryloylation or de-N-acetylation is well within the realm of routine experimentation. No evidence is of record in the instant disclosure establishing that the recited percentages of N-acryloylation or de-N-acetylation are critical for the invention. It has been held legally obvious and within the routine skill in the art to optimize a result effected variable. In the instant case, the percent N-acryloylation or de-N-acetylation of the polysaccharide or oligosaccharide in the claimed conjugate is clearly a result effected variable, and it would have been obvious to one of ordinary skill in the art at the time of the invention to vary or optimize the percent N-acryloylation or de-N-acetylation of the polysaccharide or oligosaccharide in Pons' conjugate as modified by Blake *et al.* to 50% or 95% by routine experimentation to produce the instant invention. That Pon's conjugate as modified by Blake elicits colominic acid-specific IgG or IgM antibody, and "protective antibodies", for example, anti-protein protective antibodies, is implicit from the combined teachings of the prior art.

Claims 1-4, 11-14, 16, 17, 19-22, 26-28, 37-39 and 59-63 are *prima facie* obvious over the prior art of record.

Relevant Prior Art

41) The prior art made of record and not relied upon in any of the rejections is considered

pertinent to Applicants' disclosure:

- Baumann *et al.* (*Biochemistry* 32: 4007-4013, 1993) teach an N-acryloylated alpha (2->8) polysialic acid synthesized by de-N-acetylating the polysaccharide and treating the de-N-acetylated polysaccahride with acryloyl chloride as taught by Roy and Pon (1990). See paragraph bridging pages 4007 and 4008. Baumann *et al.* further teach producing alpha (2->8) polysialic acid conjugates by "direct coupling" with the epsilon-aminolysine residues of a protein such as TT monomer. See page 4008, left column.
- Kabat *et al.* (*J. Exp. Med.* 164: 642-654, 1986) taught the protective efficcay of H46 antibody in an animal model of *E. coli* K1 infection (see entire document, especially Table 1).

Remarks

42) Claims 1-5, 8-28, 37-40 and 59-63 stand rejected. Claims 3, 4, 15, 17, 38 and 39 objected to for including non-elected subject matter.

43) The Applicants' amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** Applicants are reminded of the extension of time policy as set forth in 37 C.F.R 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

44) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center located in Crystal Mall 1. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The CM1 facsimile center's telephone number is (703) 308-4242. The RightFax number for submission of before-final amendments is

(703) 872-9306. The RightFax number for submission of after-final amendments is (703) 872-9307.

45) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (703) 308-9347. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 7.45 a.m to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

October, 2002

S. DEVI, PH.D.
PRIMARY EXAMINER